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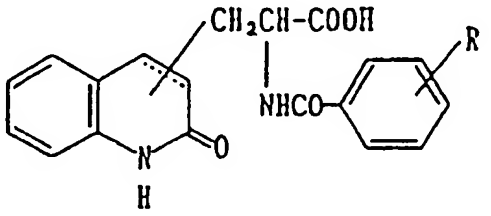
(54) Title: ADP-RIBOSYLTRANSFERASE INHIBITOR

(57) Abstract

The present invention provides a novel ADP-ribosyltransferase inhibitor containing, as the effective ingredient, a carbostyril derivative represented by general formula (I) (wherein R is a halogen atom) or a salt thereof.



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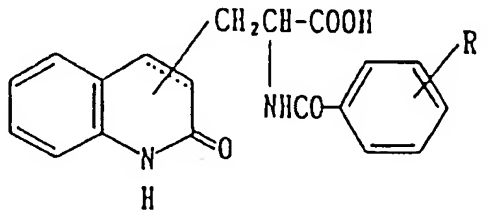
DESCRIPTION

ADP-RIBOSYLTRANSFERASE INHIBITOR

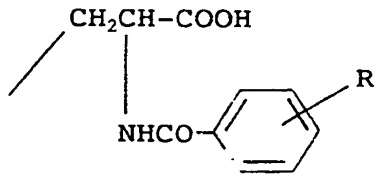
TECHNICAL FIELD

The present invention relates to an ADP-ribosyltransferase inhibitor which comprising, as the effective ingredient, a carbostyril derivative represented by the general formula (I),



(I)

[wherein R is a halogen atom (a fluorine atom, a chlorine atom, a bromine atom or an iodine atom); the side-chain of the formula,



is substituted at 3- or 4-position in the carbostyril skeleton; further the carbon-carbon bonding between 3- and 4-positions in the carbostyril skeleton is a single

bond or double bond], or a salt thereof, preferably 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or salt thereof. More particularly, the invention relates to an agent for curing infectious diseases caused by Helicobacter pylori and an agent for curing infectious diseases caused by vivoendotoxin type bacteria, on the basis of the activity for inhibiting ADP-ribosylation according to the present invention.

BACKGROUND ART

The carbostyril derivatives represented by the general formula (I) and a process for preparing the same are disclosed in JP-B-63-35623 (1988), and these derivatives are also known as useful anti-ulcerative agents. International Publication No. WO95/12579 discloses the usefulness of the carbostyril derivatives as agents for curing gastritis. JP-A-3-74329 (1991) discloses that these compounds are useful as agents for curing stomatitis and JP-A-3-145468 (1991) discloses processes for producing those carbostyril derivatives having optical activities.

Further, the inhibitory effect of carbostyril derivatives of the present invention on reactive oxygen metabolites is described in Japan. J. Pharmacol., Vol. 49, pp. 441-448 (1969), and the protectability of gastric mucous membrane by carbostyril derivatives of the present invention is described in Folia Pharmacol. Japon., Vol. 97, pp. 371-380 (1991).

Furthermore, the usefulness of carbostyril derivatives as agents for curing diabetes mellitus is described in International Publication No. WO 92/21342, the usefulness of carbostyril derivatives as agents for protecting the intestinal mucosa from disorders is described in International Publication No. WO 94/12182, and the usefulness of carbostyril derivatives as agents for inhibiting the reduction in secretion of somatostatin is described in International Publication No. WO 93/23043. The usefulness of carbostyril derivatives as agents for inhibiting carcinogenesis is described in International Publication No. WO 97/09045, and the usefulness of carbostyril derivatives as agents for curing opthalmological diseases is described in International Publication No. WO 97/13515.

ADP-ribosylation is one of the reactions of protein modification, thus, ADP-ribose moiety is cut out from coenzyme NAD by the action of toxins, then ADP-ribose moiety translocates to the target protein.

Thus, NAD, which is usable for ADP-ribosylation, has the paticular molecular structure wherein ADP-ribose moiety is bonded to nicotinamide, and the reaction for translocating ADP-ribose moiety to the target protein is called as ADP-ribosylation. This reaction was discovered in 1968 as the reaction in which diphtheria toxin acts as the catalyst. The target protein of diphtheria toxin is called as EF-2 (a peptide chain elongation factor in case of eukaryotic cell,

while it is called as EF-TU in case of procryotic cell). When EF-2 is subjected to ADP-ribosylation, then elongation of peptide chain in the ribosome is suspended, because the function of EF-2 loses by ADP-ribosylation, and the cell death is occurred.

After discovery of ADP-ribosylation reaction, various research works were made and reported as follows:

(1) when the peptide chain elongation factor of EF-2 is inhibited according to ADP-ribosylation caused by the action of diphtheria toxin or exotoxin A of Pseudomonas aeruginosa, then the biosynthesis of protein is suspended and the cell injury may be occurred;

(2) Helicobacter pylori secretes vacuolating cytotoxin which is a toxin inducing the cell death, and said vacuolating cytotoxin accelerates ADP-ribosylation, such status is regarded as pathologic symptoms especially the inducement of ulceration caused by Helicobacter pylori;

(3) cholera toxin or heat-labile enterotoxin of enterotoxigenic Escherichia coli continuously activates adenylate cyclase by ADP-ribisylating Gsα which is one of the GTP binding proteins, and increases the concentration of cAMP in the enteroepitherial cell, which promotes secretion of a large quantity of water and electrolytes, and induces hydragogue.

In recent years, various research works have

been made relating to Helicobacter pylori. In 1983, a helical bacillus was isolated from a human gastric mucosa and was successfully cultivated by Warren and Marshall of Australia [Warren, J. R. and Marshall, B. J.: Lancet, 1, 1273-1275, (1983)] and the relation between Helicobacter pylori and the lesion of gastric mucosa have gradually become evident. Further, there have been known that infectious diseases caused by Helicobacter pyloir are related not only to gastritis and peptic ulcer, but also to gastric cancer [Nomura, A., Stemmerman, G. N., Chyou, P. H., et al,: N. Engl. J. Med., 325, 1132, (1991)] and gastric lymphoma [Hussell, T., Issacson, P. G., Crabtree, J. E. and Spencer, J.: Lancet, 342, 571, (1993)].

Humectations of the phlogocyte observed in neutrophil leukocytes of a gastric ulcer patient who is diagnosed as "positive" to Helicobacter Pylori, there was not observed any significant difference between the gastric antrum and the body of stomach, except that highly shaped humectation at the margin of ulcer may be shown in the period of activation. In the period of cicatrization, outstanding reduction of humectation of the phlogocyte was observed in every sites of the stomach when Helicobater pylori was removed successfully [Asaka, M. Kudo, M., Kimura, T., et al.: Gastroenterol., 29 (Suppl. 7), 100-104, (1994)]. From these results, it is suggested that, as far as Helicobacter pylori exists in the stomach, the recurrence of peptic ulcer may be

easily occurred, even though the peptic ulcer were cured.

There are reported that a number of pathologic factors are relating to the formation of gastric mucosa disturbance caused by Helicobacter pylori, and as to one of these factors, the secretion of vacuolating cytotoxin is noticed. Thus, vacuolating cytotoxin, which is a toxin capable to induce the vacuolated degeneration as well as the cell deaths of HeLa cells and Vero cells, is secreted in the supernatant fluid of culturing Helicobacter pylori, [Leunk, R. D., et al.: J. Med. Microbiol., 26, 93-99, (1988)], further, said vacuolating cytotoxin was detected in highly frequency from the supernatant fluid of the culturing Helicobacter pylori which was isolated from the patient who has previous history of peptic ulcer, [Figura, N., et al.: J. Clin. Microbiol., 27, 225, (1989)].

The gene (i.e., vac A gene) of the above-mentioned vacuolating cytotoxin, which is noticed mostly as the pathogenic factor of Helicobacter pylori, is coding the precursor protein having the molecular weight of 139 kDa, containing a signal sequence consisting of 33 of amino acids, 87 of cytotoxin and bacterial adventitial protein having the molecular weight of 50 kDa, [Phadnis, S. H., et al.: Infect. Immunol., 62, 1557-1565, (1994)]. Telford et al. tried oral administration with 5 μg of the refined product of this vacuolating cytotoxin to a mouse of Balb/C strain, and

observed the formation of ulcer, [Telford, J. L. et al.: J. Exp. Med., 179, 1653-1658, (1994)]. As explained the above, such cytotoxin accelerates ADP-ribosylation of proteins in the presence of NAD.

There are known the facts that Helicobacter pylori secretes vacuolating cytotoxin, which induces gastric mucosa disturbance, gastritis, peptic ulcers, and gastric cancers. However, at the present stage, complete methods for removing Helicobacter pylori and for detoxification of the cytotoxin have not been found yet. Further, it is reported that the rate of infection with Helicobacter pylori in adults exceeds more than 70%, and the counterplan thereagainst should be established urgently. In case of that if the activation of vacuolating cytotoxin produced by Helicobacter pylori can be inhibited and detoxicified, then it is considered that infectious diseases caused by Helicobacter pylori can be cured more easily. Under the circumstances, development of drugs capable to control the activity of such cytotoxins and inhibit ADP-ribosylation of protein are earnestly expected.

According to the statictics of WHO (World Health Organization) in 1990, 1/3 of the total deaths in the World represents infectious diseases. Among them, the deaths caused by acute infectious diseases of the respiratory system, diarrhea and tuberclosis are most large numbers, reportedly the deaths reaches almost 10 million a year by these three infectious diseases. In

recent years, due to an increasing of international transportations and a trend towards high-speed of the vehicles, the movement of peoples among the countries are increasingly occurred frequently. The problem that might arise from the movement of peoples is diffusion of serious infectious diseases. Particularly, as to intestinal infectious diseases so-called "travellers' diarrhea", which are frequency of overt infectious diseases caused by the pathogens involving entero-toxigenic Escherichia coli, genus Salmonella, pathogenic genus Vibrio (e.g., Vibrio cholera, Vibrio para-haemolyticus), genus Shigella, genus Campylobacter and the like.

Among these infectious diseases caused by vivoendotoxin type bacteria, cholera is very serious disease of high mortality rate caused by infection of Vibrio cholera, with very severe hydragogue as the main symptoms. The pathogenetic mechanism of hydragogue is understood as follows:

(1) orally taken Vibrio cholera is adhered and fixed on the small intestine mucosa;

(2) Vibrio cholera produces CT (cholera toxin);

(3) CT activates adenylate cyclase in the enteroepitherial cells;

(4) increasing the concentration of cAMP; and

(5) hydragogue, which is the main symptom of cholera, is occurred through the action of cAMP-

dependent CI-channel (CFTR).

Thus, cholera toxin and Bordetella pertusis toxin are toxins which inhibit the transmission of biological information in down stream by ADP-ribosylating G-protein. [G-protein is a protein specifically bonds guanine nucleotides (GTP=guanosine 5'-triphosphate and GDP=guanosine 5'-diphosphate).] [IIDA Tetsuya, YOAKE Jun, HONDA Takeshi: BYOUTAI-SEIRI (Pathophysiology), 14, (3), 181-186, (1995)].

Cell response phenomena caused by a toxin are shown in the number of receptors in the system wherein the receptor stimulation is varied for increasing or inhibiting the activity of adenylate cyclase through GTP-binding protein having accelerative (Gs) and inhibitory (Gi) properties. From this system, the concentration of cyclic AMP (cAMP) in the cell is increased or decreased, then the activity of cAMP-dependent protein phophorylated enzyme (A-kinase) changes, and a functional protein is introduced by phosphorylation.

Cholera toxin is a typical A-B type toxin which is consisting of A-subunit having the activity, and B-subunit relating to the bonding to a receptor. A-subunit is consisting of A1 peptide having the molecular weight of 21.8 kDa and A2 peptide having the molecular weight of 5.4 kDa, both of which are connected to each other by S-S bonding.

On the other hand, B-subunit having the

molecular weight of 11.6 kDa and 5 of B-subunits are connected to one A-subunit. The activity of cholera toxin exhibited by A1 peptide, and the S-S bonding between A1 peptide and A2 peptide should necessarily be reduced. B-subunit combines with the cell through GM1 ganglioside on the cell membrane as the receptor, then CT (cholera toxin) connecting to GM1 is taken into the cell by the action of endocytosis through B-subunit. A1 peptide of cholera toxin makes ADP-ribosylation of α-subunit in the trimer of G protein (Gs), then this ADP-ribosylated α-subunit activates adenylate cyclase of the effector.

Cholera toxin (A1 peptide) makes ADP-ribosylation of α-subunit of Gs (i.e., A1 peptide possesses the activity of ADP-ribosyltransferase which can be cut out ADP-ribose group from NAD, and ADP-ribose translocates to the target protein), according to this ADP-ribosylation of Gsα by CT, adenylate cyclase is maintained in an activated state, because the activity of GTPase of Gsα is controlled. As the result, the concentration of cAMP in the cell is continuously increased. For this reason, the absorption of water, through the co-transportion system of Na^+-Cl^- on the intestinal inside cell membrane, is inhibited and at the same time, the secretion of Cl^- ion through Cl^- channel is accelerated, and as a whole, an overhydration (excessive secretion of the body fluid) may be occurred on inside of the intestine. Therefore, if the activity

of cholera toxin produced by Vibrio cholera can be inhibited and detoxificated, then fundamental method for curing cholera can be established.

In these intestinal infectious diseases caused by the above mentioned various vivoendotoxin type bacteria are related to ADP-ribosylation, therefore if the activity of ADP-ribosyltransferase can be inhibited, then such infectious diseases can be cured fundamentally. Thus development of an agent capable to inhibit the activity of ADP-ribosyltranferse is earnestly expected.

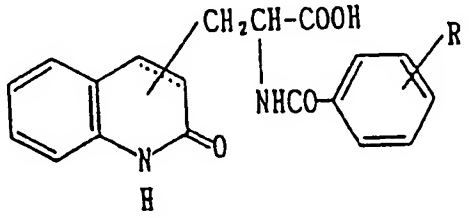
As explained the above, ADP-ribosylating reaction concerns various pathologic symptoms, particularly it relates to the actions of exotoxins. Therefore, various infectious diseases induced by said ADP-ribosylation can be cured by inhibiting said ADP-ribosylating reaction. However, until now, RG tannin which was separated and refined from the extract of Rhei Rhizoma was the only known as an agent for inhibiting ADP-ribosylation, so that development of safty and effective agent for inhibiting ADP-ribosylation is expected.

DISCLOSURE OF THE INVENTION

In consideration of the above-mentioned facts, the present inventors have made an extensive research work to find an effective agent having the activity for inhibiting ADP-ribosyltransferase. As the result, the present inventors have found the fact that a carbostyril

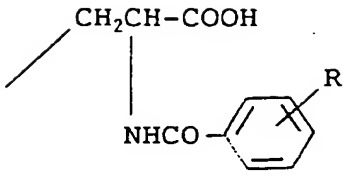
derivative represented by the general formula (I), especially 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or salt thereof shows an excellent activity for inhibiting ADP-ribosyltransferase and is useful for curing infectious diseases caused by Helicobacter pylori and for curing infectious diseases caused by various vivoendotoxin type bacteria, and finally the present invention was successfully completed.

Thus, the present invention provides an agent for inhibiting ADP-ribosyltransferase, agent for curing infectious diseases caused by Helicobacter pylori and agent for curing infectious diseases caused by vivo-endotoxin type bacteria containing, as the effective ingredient, a carbostyril derivative represented by the general formula (I),



(I)

[wherein R is a halogen atom (a fluorine atom, a chlorine atom, a bromine atom or an iodine atom); the side-chain of the formula,



is substituted at 3- or 4-position in the carbostyril skeleton; further the carbon-carbon bonding between 3- and 4-positions in the carbostyril skeleton is a single bond or double bond] or a salt thereof, preferably 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

The carbostyril derivative of the present invention inhibits the activity of ADP-ribosyl-transferase and is capable to improve various pathological symptoms caused by ADP-ribosylation of proteins.

The carbostyril derivative of the present invention is useful as an agent for curing infectious diseases caused by Helicobacter pylori, because said derivative is capable to control the activation of vacuolating cytotoxin by inhibiting the activity of ADP-ribosyltransferase. Concretely, the carbostyril derivative improves various pathological syndromes, for example, ulcer caused by Helicobacter pylori.

Furthermore, the carbostyril derivative of the present invention improves various infectious diseases caused by vivoendotoxin type bacteria represented by

enterotoxigenic Escherichia coli, genus Salmonella, pathogenic genus Vibrio (e.g., Vibrio cholera and Vibrio parahaemolyticus), genus Shigella, genus Campylobacter and the like. That is, the carbostyril derivative of the present invention is useful as agents for curing infectious diseases caused by vivoendotoxin type bacteria, because the carbostyril derivative inhibits the activity of ADP-ribosyltransferase. For example, in case of infectious disease caused by Vibrio cholera, the carbostyril derivative inhibits ADP-ribosylation of cholera toxin and controls the activity of adenylate cyclase.

The ADP-ribosyltransferase inhibitor of the present invention can be prepared in the form of combined drugs by formulating the carbostyril derivative represented by the general formula (I) or salt thereof with antibiotics.

In case of preparing an agent for curing infectious diseases caused by Helicobacter pylori, a carbostyril derivative of the general formula (I) or salt thereof can be used in the form of a combined drug jointly with antibiotics for example, Clarithromycin, Metronidazole, Tinidazole, Amoxicilline and the like. Further, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or salt thereof can be used jointly in combination with Clarithromycin and Metronidazole; in combination with Clarithromycin and Tinidazole; in a combination with Clarithromycin and Amoxicillin; and the

like.

In case of preparing an agent for curing infectious diseases caused by vivoendotoxin type bacteria, the carbostyril derivative of the general formula (I) or salt thereof can be used in the form of a combined drug jointly with antibiotics, for example newer quinoline type antibiotics such as Nafloxacin, Enoxacin, Ofloxacin, Ciproxacin, Lomefloxacin, Tosufloxacin, Sparfloxacin, Levofloxacin and the like; and tetracycline type antibiotics such as Tetracycline, Tetracycline hydrochloride, Tetracycline metaphosphite, Oxytetracycline hydrochloride and the like.

Among compounds represented by the general formula (I), a compound having acidic group can form a salt with pharmaceutically acceptable basic compound. As to such basic compound for example, metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide and the like; carbonates or bicarbonates of alkali metals such as sodium carbonate, sodium hydrogencarbonate and the like; alkali metal alcoholates such as sodium methylate, potassium ethylate and the like can be exemplified. Furthermore, among compounds represented by the general formula (I), a compound having bsic group can form a salt with common pharmaceutically acceptable acid. As to such acid for example, inorganic acids such as sulfuric acid, nitric acid, hydrochloric acid, hydrobromic acid and the like; organic acids such as acetic acid, p-toluenesulfonic

acid, ethanesulfonic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, benzoic acid and the like can be mentioned. These salts can also be used, similar to compounds represented by the general formula (I) in free form, as compounds of effective ingredient in the present invention. Moreover, compounds represented by the general formula (I) involve inevitably their stereoisomers and optical isomers, and these isomers can also be used as compounds of effective ingredients.

In the present invention, an ADP-ribosyltransferase inhibitor, an agent for curing infectious diseases caused by Helicobacter pylori and an agent for curing infectious diseases caused by vivoendotoxin type bacteria are prepared in the form of general types of pharmaceutical preparations by formulating a carbostyril derivative of the general formula (I) or a salt thereof, and if necessary it can be used in combination with the above-mentioned antibiotics. These pharmaceutical preparations of the present invention can be prepared into various forms of common pharmaceutical preparations by formulating with commonly employed diluents or excipients, such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants and the like. The pharmaceutical preparations can be shaped into various forms depending upon the curing purposes, thus, typical examples of the forms are tablets, pills, powders, liquid medicines, suspensions, emulsions,

granules, capsules, suppositories, injection preparations (liquid, emulsion, suspension and the like), and syrup preparations. Further, sustained release preparations can also be prepared by formulating with suitable resins.

For the purpose of shaping in the form of tablets, any known carriers which are used widely in this field can be applied, for example, excipients such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid and the like; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone and the like; disintegrators such as dry starch, sodium alginate, agar powder, laminalia powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceride of stearic acid, starch, lactose and the like; disintegration inhibitors such as white sugar, stearin, cacao butter, hydrogenated oils and the like; absorption accelerators such as quaternary ammonium base, sodium lauryl sulfate and the like; humectants such as glycerin, starch and the like; adsorbents such as starch, lactose, kaolin, bentonite, colloidal silicic acid and the like; lubricants such as refined talc, stearic acid salts, boric acid powder,

polyethylene glycols and the like. In case of necessity, the tablets can be prepared in the form of common coated tablets, for example, sugar-coated tablets, gelatin film-coated tablets, enteric film-coated tablets, film-coated tablets, or in the form of double-layers tablets, multiple-layers tablets and the like.

For the purpose of shaping into the form of pills, any known carriers which are widely used in this field can be applied, for example, excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and the like; binders such as arabic gum powder, tragacanth gum powder, gelatin, ethanol and the like; and disintegrators such as laminaria, agar-agar and the like can be exemplified.

For the purpose of shaping into the form of suppositories, any known carriers which are widely used in this field can be applied, for example, polyethylene glycols, cacao butter, higher alcohols, esters of higher alcohol, gelatin, semi-synthesized glycerides and the like can be exemplified.

For the purpose of shaping into the form of injection preparations, they can be prepared to solutions, emulsions or suspensions. Generally they are sterilized and preferably made isotonic to the blood. In preparing the injection preparations as in the form of solutions, emulsions or suspensions, any known diluents which are widely used in this field can be

applied. For example, water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, fatty acid esters of polyoxyethylene sorbitan and the like can be exemplified. In the case of make the injection preparations isotonic to the blood, sufficient amount of sodium chloride, glucose or glycerin may be contained therein. Additionally, a dissolving adjuvant, a buffer solution, an analgesic agent and the like which are commonly used may be contained therein. In case of necessity, a coloring agent, a preservative, a perfume, a flavoring agent, a sweetening agent and other medicines may be contained therein.

Preparations for external use are prepared in the form of common pharmaceutical preparations for external use.

As to common pharmaceutical preparations for external use are including, for example, a liquid medicine, a medicinal oil, a lotion, a liniment, an oleaginous ointment, an emulsion type ointment, such as O/W type hydrophilic ointment and W/O type water-absorbing ointment, a water-soluble ointment, a pasta, a plaster, a patch, a cream, an emulsion and the like, and these forms of pharmaceutical preparations for external use are not restricted within the scope of these examples. Each one of these forms of pharmaceutical preparations for external use can be prepared by common methods.

In shaping of these preparations for external use, various base materials which are widely used in this field can also be applied. For example, at least one oleaginous base can be used singly, or mixture of two or more of them can be used widely; or at least one water-soluble ointment base can be used singly, or mixture of two or more of them can be used widely. Specific examples of these ointment base are fats and oils such as peanut oil, sesame oil, soybean oil, safflower oil, avogado oil, sunflower oil, corn oil, rapeseed oil, cotton seed oil, castor oil, camellia oil, coconut oil, olieve oil, poppy seed oil, cacao butter, beef tallow, lard, wool fat and the like; modified bases obtained by subjecting these fats and oils to chemical changes such as hydrogenation; mineral oils such as petrolatum, paraffin, silicone oil, squalane and the like; higher fatty acid esters such as isopropyl myristate, n-butyl myristate, isopropyl linoleate, acetyl ricinoleate, stearyl ricinoleate, propyl ricinoleate, isopropyl ricinoleate, isobutyl ricinoleate, heptyl ricinoleate, diethyl sebacate and diisopropyl adipate; higher aliphatic alcohols such as cetyl alcohol and stearyl alcohol; and waxes such as bleached bees wax, spermaceti, Japan wax, lanolin, carnauba wax, shellac wax and the like; higher fatty acids such as stearic acid, oleic acid, palmitic acid and the like; mixtures of mono-, di- and tri-glycerides of saturated or unsaturated fatty acids having 12 to 18 carbon

atoms; polyhydric alcohols such as ethylene glycols, polyethylene glycols, propylene glycol, polypropylene glycols, glycerin, batyl alcohol, pentaerythritol, sorbitol, mannitol and the like; gummy substances such as arabic gum, benzoin gum, guaiacum, tragacanth gum and the like; water-soluble natural high molecular compounds such as gelatin, starch, casein, dextrin, pectin, sodium pectate, sodium alginate, methyl cellulose, ethyl cellulose, carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, nitrocellulose, crystalline cellulose and the like; water-soluble synthetic high molecular compounds such as polyvinyl alcohol, poly-(vinyl methyl ether), polyvinylpyrrolidone, sodium polyacrylate, carboxyvinyl polymer, polyethyleneimine and the like; nonionic, anionic, amphoteric and cationic surfactants; ethanol, isopropanol and water, can be exemplified.

To the pharmaceutical preparations for external use, there can be added common additives such as a gelling agent, a preservative, an antioxidant, a buffering agent, a pH controlling agent, a wetting agent, an antiseptic agent, a coloring agent, a flavoring agent, a pigment, a thickening agent, a metal chelating agent and the like.

Aerosol type preparations can be prepared generally by formulating a sterilized solution or suspension of the carbostyril derivative of the general formula (I) with a propellant. In case of preparing in

the form of a solution or suspension, any one of known diluents which are commonly used in this field can also be used, thus the diluents which are exemplified in formulating the injection preparations can be used. As to the propellant, any one of the propellants which are commonly used in this field can also be used, thus, chlorofluorocarbons such as Fron-12 or Fron-123; compressed gas propellants such as nitrogen gas and carbon dioxide and the like can be exemplified. The aerosol type preparations may further contain a common solubilizing adjuvant, a buffering agent, and the like, and if necessary, a coloring agent, a preservative, a perfume, a flavoring agent, a sweetening agent may be added thereto.

The amount of the carbostyril derivative of the general formula (I) or salt thereof to be contained in the agent for inhibiting ADP-ribosyltrasferase of the present invention is not particularly restricted and can be selected from a wide range, and the amount may be generally selected within the range of 1-70% by weight, preferably 5-50 % by weight.

Method for administering ADP-ribosyltransferase of the present invention is not particularly restricted, except that in the case to be selected specifically for the particular treating purpose. The method is decided depend upon the form of preparation, the age of patient, the distinction of sex and other relating conditions, the degree of disease condition of

the patient and others. For example, tablets, pills, a liquid medicine, a suspension, an emulsion, granules, a syrup and capsules are administered orally. An injection preparation is administered intravenously singly or in combination with common auxiliary solutions such as glucose solution and/or amino acid solution. In case of necessity, it is singly administered intramuscularly, intradermally, subcutaneously or intraperitoneally. A suppository is administered intrarectally. A preparation for external use is coated on the diseased part of the body.

Dosage of the ADP-ribosyltransferase inhibitor of the present invention may be suitably selected depend upon the age of patient, the distinction of sex and other conditions, the degree of disease condition of the patient as well as other related factors, and generally the amount of carbostyril derivative of the general formula (I) or a salt thereof may be administered about 0.6 to 50 mg per 1 kg of the body weight per day. The desirable content of the effective ingredient in each unit of the administration form may be 10 to 1,000 mg.

EXAMPLE

The present invention will be explained more specifically by showing Preparation Examples and Pharmacological Tests.

Preparation Example 1

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	150 g
Avicel (trade name for microcrystalline cellulose, manufactured by Asahi Chemical Industry Co., Ltd.)	40 g
Corn starch	30 g
Magnesium stearate	2 g
Hydroxypropylmethyl cellulose	10 g
Polyethylene glycol 6000	3 g
Castor oil	40 g
Methanol	40 g

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid, Avicel, corn starch and magnesium stearate were mixed together and ground, then this mixture was shaped into tablet form by using a tablet machine with a punch (R 10 mm). Thus obtained tablets were coated with a film-coating agent consisting of hydroxypropylmethyl cellulose, polyethylene glycol 6000, caster oil and methanol, to prepare film-coated tablets.

Preparation Example 2

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	150.0 g
Citric acid	1.0 g
Lactose	33.5 g
Dicalcium phosphate	70.0 g
Pluronic F-68	30.0 g

Sodium lauryl sulfate	15.0 g
Polyvinylpyrrolidone	15.0 g
Polyethylene glycol (Carbowax 1500)	4.5 g
Polyethylene glycol (Carbowax 6000)	45.0 g
Corn starch	30.0 g
Dry sodium lauryl sulfate	3.0 g
Dry magnesium stearate	3.0 g
Ethanol	A sufficient quantity

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid, citric acid, lactose, dicalcium phosphate, Pluronic F-68 and sodium lauryl sulfate were mixed together.

The mixture was sieved through a No. 60 screen, the resulting sieved mixture was wet-granulated with an ethanol solution containing polyvinyl pyrrolidone, Carbowax 1500 and Carbowax 6000. In case of necessity, ethanol was added to convert the mixture into a paste-like mass. Corn starch was added, and mixing operation was continued until uniform particles were formed. The resulting particles were passed through a No. 10 screen, then placed in a tray, and were dried in an oven at 100°C for 12-14 hours. The dried particles were sieved through a No. 16 screen. Next, dry sodium lauryl sulfate and dry magnesium stearate were added to the resulting particles. The mixture was compressed into core tablets of the desired shape by using a tablet

machine. The resulting core tablets were treated with a varnish and then talc powder was sprayed thereon for preventing from moisture absorption. On the surface of resulting core tablets, undercoat layer was coated. Sufficient number of varnish coatings were conducted to the core tablets so as to make them suitable for internal use. Formation of undercoat layer and smooth coating were conducted to make the coated tablets having completely round shape and smooth surface. Color coating was conducted until the desired color surface was obtained. After drying, the coated tablets were polished to obtain tablets of uniform gloss.

Preparation Example 3

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	5.0 g
Polyethylene glycol (Mol. wt.: 4000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methylparaben	0.18 g
Propylparaben	0.02 g
Distilled water for injection	10.0 ml

Parabens, sodium metabisulfite and sodium chloride were dissolved in a half volume of the above mentioned distilled water for injection at 80°C under stirring. The resulting solution was cooled to 40°C,

then to this solution were added 2-(4-chlorobenzoyl-amino)-3-(2-quinolon-4-yl)propionic acid, polyethylene glycol and polyoxyethylene sorbitan monooleate and dissolved. Next, the remaining a half volume of distilled water was added to the resulting solution to make the solution to the final volume. Thus obtained solution was sterilized by passing through a suitable filter paper to prepare the desired injection preparation.

Pharmacological Tests

Test Example 1 Inhibition test of ADP-ribosyltransferase (Determination of ADP-ribosylation of P70 protein and Agmatine)

Main toxicological action of cholera toxin (CT) is known that it makes ADP-ribosylation of Gsα which is one of the G-proteins in the cell. The test was conducted to know whether or not 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid (hereinafter referred to as "Test compound") inhibits ADP-ribosylation of a G-protein by using a membrane fraction of Caco-2 cells originated from carcinoma of colon.

Inhibition test of ADP-ribosylation of P70 protein and Agmatin by using CT was conducted by procedure according to the method reported by Morinaga, et al. [Morinaga, N., Noda, M. and Kato, I.: FEBS Letters, 271, 211, (1990)]. Thus, into a reaction

liquid consisting of 1 μM of [α-^{32}P]NAD (2 μCi), 10 mM of thymidine, 1 mM of EDTA, 5 mM of dithiothreitol (DTT) and 50 mM of potassium phosphate buffer solution (pH 7.5), was added 100 μg of P70 protein or Agmatine, 2.5 μg of cholera toxin A (CTA) and 1 mM of "Test compound". Then the whole mixture was reacted at 37°C for 1 hour. Trichloroacetic acid was added to the reaction mixture to obtain precipitate, then conducted an SDS-polyacrylamide gel electrophorasis. Radioactivity of the gel was determined by use of BIO-Imageing Analyser. In conducting the control test, reaction was conducted similarly, except that "Test compound" was not used.

As the result, when CTA was added, then ADP-ribosylation of P70 protein and Agmatine were occurred, and intake of ^{32}P was observed. However, when "Test compound" was added, then there was observed remarkable inhibition of ADP-ribosylation of each one of the proteins.

Test Example 2 Inhibition test of ADP-ribosylation of 70 kDa protein of Helicobacter pylori

(1) Preparation of extract of Helicobacter pylori cell body

Helicobacter pylori was cultivated on an agar culture of Brucella agar (5% fetal calf serum was added) for 2 days. Cultivated cell bodies of bacteria on the agar plate was taken by scratching with sterilized swab and was suspended in 90 ml (placed in a flask of 500 ml

capacity) of a Brucella broth (5% fetal calf serum was added), then the suspension was subjected to shaking culture under a slightly aerobic condition for 24 hours. Then cultivated cell bodies of bacteria in the culture fluid were collected by filtration and were suspended in 10 nM tris-HCl solution (pH 7.5), then the suspension was shaken for 30 minutes. The cell bodies of bacteria were removed by centrifugal separation and filtration by use of a filter (pore diameter: 0.2 μm) and obtained a crude extract of cell bodies of Helicobacter pylori.

(2) ADP-ribosylation

40 Microliters of the obtained crude extract of cell bodies (containing 300-500 μg/ml of protein) was added to 100 mM of tris-HCl [pH 7.5, containing 1 mM of EDTA, 10 mM of $MgCl_2$, and 1 μM of [α-^{32}P]NAD (2 μCi)] to make the total volume of 200 μl, and reacted at 37°C for 10 minutes, then 800 μl of 10%-trichloroacetic acid was added to the mixture to cease the reaction.

Thus obtained reacted mixture was subjected to centrifugal separation at 15,000 rpm for 10 minutes, then the precipitate obtained was dissolved in a sample buffer solution for SDS-PAGE (sodium dodecylsulfate-polyacrylate gel electrophorasis) (containing 50 mM of tris-HCl, pH 6.8, 2% of SDS, 10% of glycerol, 0.01% of bromophenol blue, 100 mM of dithiothreitole), and subjected to heat-treatment at 80°C for 10 minutes.

The heat-treated sample fluid was subjected to an electrophoresis by using 10% SDS-polyacrylamide gel,

then the intake of radioactivity into the colored protein in the gel was quantitatively analyzed by use of Bioimage Analyzer (manufactured by Fuji Photo Film Co., Ltd.). The position of 70 kDa protein on the gel was determined in terms of the position of molecular weight marker on the electrophoresis conducted at the same time [Cf., Morinaga, N. I., Noda, M. and Kato, I., FEBS Letters, 271, 211, (1990)].

In the above-mentioned test, 2-(4-chloro-benzoylamino)-3-(2-quinolon-4-yl)propionic acid was used as the test compound, and an aqueous solution having various concentrations of the test compound was added to each one of the above-mentioned reaction systems, and distilled water was used as a control.

Activity for inhibiting ADP-ribosyltransferase performed by the test compound was shown as the relative activity in terms of that the value of control test was defined as 100%. The results are shown in Table 1. As can be seen from Table 1, the carbostyril derivative of the present invention clearly inhibits the ADP-ribosylation of the protein 70 kDa of Helicobacter pylori, thus the carbostyril derivative of the present invention possesses activity for inhibiting ADP-ribosyltransferase.

Table 1

Concentration of Test compound (mM)	Relative activity (%) ± SD
0.0	100.0 ± 5.0
0.2	68.7 ± 1.0
0.5	61.2 ± 2.9
1.0	52.9 ± 4.7
2.0	41.9 ± 3.3
5.0	24.2 ± 6.3

Test Example 3 Agmatine assay

Agmatine assay was conducted according to the method reported by Noda, et al., [Kato I., Noda M.: ADP-ribosylation of cell membrane proteins by Staphylococcal α-toxin and leukocidin in rabbit erythrocytes and polymorphonuclear leukocytes; FEBS Letter, 281, 185-190 (1989)]. Thus, to 50 mM of potassium phosphate buffer solution (pH 7.5) [containing 5 mM of $MgCl_2$, 100 μM of guanosine triphosphate (GTP), 100 μM of [adenine-^{14}C] NAD (60000 cpm), 20 mM of dithiothreitole (DTT), 20 mM of agmatine and egg white albumin (0.1 mg/ml)] was mixed with 1 μg of A-subunit of cholera toxin (CTA) and test compound (300 μl in total volume), and reacted at 30°C for 3 hours. 50 Microliteres of this reaction mixture was taken and passed through a column (0.5 x 2 cm in size) packed with Dowec AG1-X2 (manufactured by Biorad Co.) to remove unreacted [adenine-^{14}C] NAD, then

measured the formed [adenine-^{14}C] ADP-ribosylated agmatine by counting the radioactivity. The inhibitory rate of ADP-ribosyltransferase performed by the test compound was obtained by calculating from the formation of [adenine-^{14}C] ADP-ribosylated agmatine as the index.

In this Test, similar to the above-mentioned Test Examples 1 and 2, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid was used as the test compound, and an aqueous solution having various concentrations from 0.0 to 5.0 mM of the test compound was added to each one of the reaction systems. As to the control test, distilled water was used.

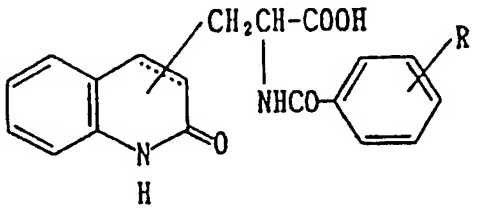
The activity for inhibiting ADP-ribosyltransferase performed by the test compound was shown as the relative activity in terms of that the value of control test was defined as 100%. The results are shown in Table 2. As can be seen from Table 2, the carbostyril derivative of the present invention clearly inhibits the ADP-ribosylation of agmatine, thus the carbostyril derivative of the present invention possesses activity for inhibiting ADP-ribosyltrasferase.

Table 2

Concentration of Test compound (mM)	Relative activity (%) ± SD
0.0	100.0 ± 3.6
0.2	98.8 ± 8.6
0.5	92.7 ± 3.3
1.0	91.6 ± 1.9
2.0	70.1 ± 2.3
5.0	16.5 ± 0.2

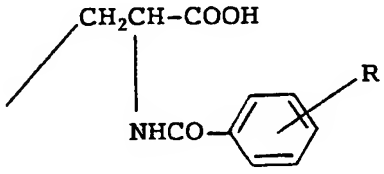
CLAIMS

1. An ADP-ribosyltransferase inhibitor which comprises as the effective ingredient, a carbostyril derivative represented by the general formula (I),



(I)

[wherein R is a halogen atom (a fluorine atom, a chlorine atom, a bromine atom or an iodine atom); the side-chain of the formula,



is substituted at 3- or 4-position in the carbostyril skeleton; further the carbon-carbon bonding between 3- and 4-positions in the carbostyril skeleton is a single bond or double bond], or a salt thereof.

2. An agent for curing an infectious disease caused by Helicobacter pylori which comprises, as the effective ingredient, the carbostyril derivative or salt

thereof as claimed in Claim 1.

3. An agent for curing an infectious disease caused by vivoendotoxin type bacteria which comprises, as the effective ingredient, the carbostyril derivative or salt thereof as claimed in Claim 1.

4. The ADP-ribosyltransferase inhibitor according to Claim 1, wherein the effective ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

5. The agent for curing an infectious disease caused by Helicobacter pylori according to Claim 2, wherein the effective ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

6. The agent for curing an infectious disease caused by Helicobacter pylori according to Claim 2, which comprises, as the effective ingredients, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or salt thereof and antibiotic(s).

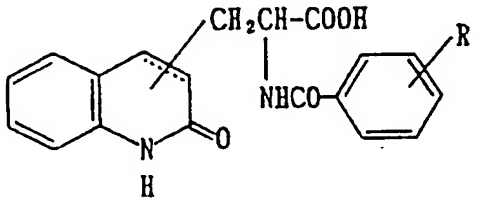
7. The agent for curing an infectious disease caused by vivoendotoxin type bacteria according to Claim 3, wherein the effective ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

8. The agent for curing an infectious disease caused by vivoendotoxin type bacteria according to Claim 7, wherein the infectious disease is an intestinal infectious disease caused by vivoendotoxin type

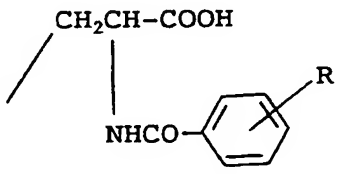
bacteria.

9. The agent for curing an intestinal infectious disease caused by vivoendotoxin type bacteria according to Claim 8, which comprises, as the effective ingredients, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or salt thereof and antibiotic(s).

10. Use of compound for the production of a medicament for inhibiting ADP-ribosylation, which comprises, as the effective ingredient, a carbostyril derivative represented by following general formula,



[wherein R is a halogen atom (a fluorine atom, a chlorin atom, a bromin atom or an iodine atom); the side-chain of the formula,



is substituted at 3- or 4-position in the carbostyril

skeleton; further the carbon-carbon bonding between 3- and 4-position in the carbostyril skeleton is a single bond or double bond] or a salt thereof.

11. The use of a compound for the production of a medicament for curing an infectious disease caused by Helicobacter pylori which comprises, as the effective ingredient, a carbostyril derivative or a salt thereof as claimed in Claim 10.

12. The use of a compound for the production of a medicament for curing an infectious disease caused by vivoendotoxin type bacteria which comprises, as the effective ingredient, a carbostyril derivative or a salt thereof as claimed in Claim 10.

13. The use of a compound for the production of a medicament for inhibiting ADP-ribosylation according to Claim 10, which comprises, as the effective ingredient, a 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

14. The use of a compound for the production of a medicament for curing an infectious disease caused by Helicobacter pylori according to Claim 11, which comprises, as the effective ingredient, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

15. The use of a compound for the production of a medicament for curing an infectious disease caused by Helicobacter pylori according to Claim 11, which comprises, as the effective ingredients, 2-(4-chloro-

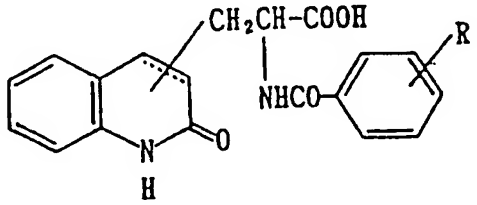
benzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof and antibiotic(s).

16. The use of a compound for the production of a medicament for curing an infectious disease caused by vivoendotoxin type bacteria according to Claim 12, wherein the effective ingredient is 2-(4-chlorobenzoyl-amino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

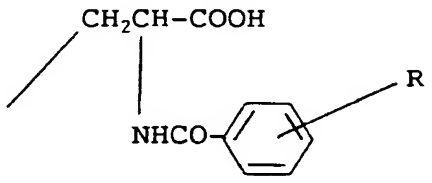
17. The use of a compound for the production of a medicament according to Claim 16, wherein the infectious disease is an intestinal infectious disease caused by vivoendotoxin type bacteria.

18. The use of a compound for the production of a medicament for curing an intestinal infectious disease caused by vivoendotoxin type bacteria according to Claim 17, which comprises, as the effective ingredients, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof and antibiotic(s).

19. Method for inhibiting ADP-ribosylation, by administering to a patient in need thereof an agent comprising, as the effective ingredient, a carbostyril derivative represented by the general formula,



[wherein R is a halogen atom (a fluorine atom, a chlorine atom, a bromine atom or an iodine atom); the side chain of the formula,



is substituted at 3- or 4-position in the carbostyril skeleton; further the carbon-carbon bonding between 3- and 4-positions in the carbostyril skeleton is a single bond or double bond] or a salt thereof.

20. The method for curing an infectious disease caused by Helicobacter pylori by administering an agent comprising, as the effective ingredient, a carbostyril derivative or a salt thereof as claimed in Claim 19.

21. The method for curing an infectious disease caused by vivoendotoxin type bacteria by administering an agent comprising, as the effective ingredient, a carbostyril derivative or a salt thereof as claimed in Claim 19.

22. The method for inhibiting ADP-ribosyltransferase according to Claim 19, wherein the effective ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

23. The method for curing an infectious disease caused by Helicobacter pylori according to Claim 20,

wherein the effective ingredient is 2-(4-chlorobenzoyl-amino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

24. The method for curing an infectious disease caused by Helicobacter pylori according to Claim 20, wherein the agent comprising, as the effective ingredients, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof and antibiotic(s).

25. The method for curing an infectious disease cause by vivoendotoxin type bacteria according to Claim 21, wherein the effective ingredient is 2-(4-chloro-benzoyl-amino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

26. The method for curing an infectious disease according to Claim 25, wherein the infectious disease is an intestinal infectious disease caused by vivoendotoxin type.

27. The method for curing an intestinal infectious disease caused by vivoendotoxin type bacteria according to Claim 26, by administering to a patient in need thereof, an agent comprising, as the effective ingredients, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof and antibiotic(s).

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/JP 97/04579

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/47 //(A61K31/47,31:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAITA ET AL.: "Combination therapy with lansoprazole, amoxicilline, and rebamipide for cure of Helicobacter pylori infection and histological gastritis in gastric ulcer patients" JPN ARCH. INT. MED., vol. 43, no. 2, 1996, pages 15-25, XP002059842 see abstract --- -/--	1-9,11, 14,15, 20,23,24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
23 March 1998	03.04.98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Gac, G

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INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/JP 97/04579

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	URAKAMI ET AL.: "Mucosa-associated lymphoid tissue (MALT) lymphoma which did not improve despite eradication therapy for Helicobacetr pylori infection, report of a case" STOMACH AND INTESTINE, vol. 31, no. 8, July 1996, pages 1027-1033, XP002059843 see english abstract page 1033 ---	1-9,11, 14,15, 20,23,24
X	WO 95 12579 A (OTSUKA PHARMACEUTICAL COMPANY LTD) 11 May 1995 cited in the application see the whole document	1-5,7,8, 11,14, 20,23
A		6,9,15, 24

X	WAKEBE ET AL.: "Suppressive reduction and improvement effects of rebamipide on gastric mucosal cell injuries induced by H. palori" GASTROENTEROLOGY, vol. 110, no. 4suppl., April 1996, page a289 XP002059844	1-5,7,8, 11,14, 20,23
A	see abstract	10,13

X	PATENT ABSTRACTS OF JAPAN vol. 0, no. 0 & JP 08 295673 A (OTSUKA PHARMACEUT. CO LTD), 12 November 1996, see abstract	1-5,7,8, 11,14, 20,23

X	HAN : "Effects of rebamipide on gastric cell damage by Helicobacter pylori-stimulated human neutrophils" PHARM. RES., vol. 32, no. 4, October 1995, pages 201-207, XP002059845 see the whole document	1-5,7,8
A		11,14, 20,23

X	WO 94 12182 A (OSTUKA PHARMACEUTICAL CO. LTD) 9 June 1994 cited in the application see the whole document	1-5,7,8

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INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/JP 97/04579

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMASAKI ET AL.: "Effect of OPC-12759, a novel antiulcer agent, on chronic and acute experimental gastric ulcer, and gastric secretion in rats" JPN J. PHARMACOL., vol. 49, no. 4, 1989, pages 441-448, XP002059846 see the whole document	1-5,7,8
P,X	YOON ET AL.: "Effect of rebamipide on eradication of Helicobacter pylori by triple therapy of omeprazole, clarithromycin & amoxicillin" GASTROENTEROLOGY, vol. 112, no. 4suppl., April 1997, page a338 XP002059847 see abstract	1-9,11, 14,15, 20,23,24
P,X	HAHM ET AL.: "New combination therapy with lansoprazol, amoxicillin, and rebamipide augments the eradication rate of Helicobacter pylori" GASTROENTEROLOGY, vol. 112, no. 4suppl., April 1997, page a137 XP002059848 see abstract	1-9,11, 14,15, 20,23
P,X	SAITA ET AL.: "Antioxidative agent (rebamipide), combined with dual therapy, helps the cure of H. pylori infection and the improvement of histological gastritis in gastric ulcer patients" GASTROENTEROLOGY, vol. 112, no. 4suppl., April 1997, page a275 XP002059849 see abstract	1-9,11, 14,15, 20,23
P,X	AIHARA ET AL.: "Evaluation of mucosal protective anti-gastrtitis and anti-gastric ulcer drug (rebamipide, MUCOSTA) against H. pylori-induced mouse model" GASTROENTEROLOGY, vol. 112, no. 4suppl., April 1997, page a54 XP002059850 see abstract	1-9,11, 14,15, 20,23

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte tional application No.
PCT/JP 97/04579

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-27
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 19-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter..onal Application No
PCT/JP 97/04579

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9512579 A	11-05-95	AU 8003194 A	23-05-95
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